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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,625	04/04/2006	Tine Hoff	10355.204-US	9296

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EXAMINER	
VOGEL, NANCY TREPTOW	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
03/22/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/574,625	HOFF, TINE	
	Examiner	Art Unit	
	NANCY VOGEL	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25,26,28,30,31,33,34,36,38,39 and 41-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 25, 26, 28, 30,31, 33, 34, 36, 38, 39, 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 23, 25, 26, 28, 30,31, 33, 34, 36, 38, 39, 41-45 are pending.

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection that were not necessitated by applicants' amendment and therefore, this action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25, 26, 28, 33, 34, 36, 38, 39, 43, 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained essentially for the reasons made of record in the previous Office action, applied to different claims as necessitated by applicant's amendment:

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of

the sequence, it is "not a sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include: (1) Actual reduction to practice, (2) Disclosure of drawings or structural chemical formulas, (3) Sufficient relevant identifying characteristics (such as: i. Complete structure, ii. Partial structure, iii. Physical and/or chemical properties, iv. Functional characteristics when coupled with a known or disclosed, and correlation between function and structure), (4) Method of making the claimed invention, (5) Level of skill and knowledge in the art, and (6) Predictability in the art.

"Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the

conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a genus of methods using a secretion stress inducible promoter, or using a secretion stress inducible promoter which is in its normal position linked to a gene encoding a polypeptide which has at least 90 or 95% identity to the amino acid sequence of SEQ ID NO:2.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 23, 25, 26, 28, 33, 34, 36, 38, 39, 43, 44 are broad and generic, with respect to all possible promoters and cells. The possible structural variations are numerous since they encompass methods using any secretion stress inducible promoter, or any promoter which normally is linked to a gene encoding any protein which has at least 90 or 95% identity to SEQ ID NO:2. Specifically, the claims lack written description because one could not predict the structure of a promoter which has the recited property. Therefore, one of ordinary skill in the art would not be able to determine which promoter would have the recited property without trial and error experimentation, and thus the structure-function correlation is considered to be unpredictable. Regarding the claims drawn to promoters normally linked to a protein having 90 or 95% identity to SEQ ID NO:2, there is no structural information recited regarding the promoter itself, and regarding the protein structure, the specification does not provide sufficient descriptive support for the myriad of proteins encompassed by the

claims, and the specification does not provide a representative number of examples of promoters normally linked to protein encoding regions having the recited identity to SEQ ID NO:2. such that one of ordinary skill in the art would be able to envision the next species of the genus of polypeptides and promoters that have the recited activity.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession *of the entire scope* of the claimed invention.

Applicant's arguments filed 1/4/11 have been considered but have not been found convincing.

Applicants have argued that they have disclosed the sequence of a single secretion stress inducible promoter, which includes the nucleic acids 1-999 of SEQ ID NO:1; or the ykdA promoter region. Applicant argues that "given the maturity of the science and that the specification provides: SEQ ID NO:1 and 2, and the language from the specification as a whole, one of skill in the art would understand that Applicants were in possession of the claimed secretion stress inducible promoters". However, it is maintained that a single secretion stress inducible promoter, does not provide a

sufficiently representative number of examples of such promoters. The genus of the claims under rejection is broad, and since it cannot be envisioned what other members of the genus would be regarding sequence, i.e. structure, it is maintained that the specification does not show possession of the entire scope of the invention as claimed. Therefore the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims23, 25, 26, 28, 30, 31, 33, 34, 36, 38, 39, 41-46 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 45, and by dependence 25, 26, 28, 30, 31, 33, 34, 36, 38, 39, 41-46 are vague and indefinite in the recitation of the term "unknown secreted protein" since it is not clear what the intended metes and bounds would be, since it is not clear which proteins, would be considered "known" or "unknown". This rejection is maintained for the reasons of record. Applicant has argued that "one of ordinary skill in the art would certainly understand that the phrase "unknown secreted protein" means that the secreted protein is not known". However, this argument merely restates the claim language, and for the reason set forth above, is not found convincing.

Claim 44 is vague and indefinite in the recitation of "the enzyme is selected from the group consisting of proteases....", since the claim is dependent on claim 23, which recites that the secreted protein [which is an enzyme] is "unknown". Therefore, it is

unclear how an unknown protein can be one of the enzymes listed in claim 44. This is a new rejection necessitated by applicant's amendments. This rejection is maintained for reasons of record. Applicant argues that the amendment to claim 44 overcomes the rejection. However , it remains unclear what is intended since if the protein or enzyme is "unknown", it is not clear how the enzyme can be one of those listed in claim 44.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 25, 26, 28, 39, 43, 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Griffith et al. (FASEB Journal, 17, No. 4-5, 2003, Abst. No. 369.8) (cited by applicants) or Griffith et al. (FEBS LETT. 2003, 553(1-2), pp. 45-50) (cited by applicants).

This rejection is maintained essentially for the reasons of record.

Griffith et al. (FASEB J) or Griffith et al. (FEBS Lett.) disclose a method in which host cells are provided, comprising a gene library and a reporter gene operably linked to a "secretion stress" promoter, the host cell is cultured, and a host cell is selected which expresses the reporter protein and comprises the gene. The activity of the

unfolded protein response (UPR) is monitored using a UPR element-lacZ fusion. This response is considered equivalent to "secretion stress". Griffith et al. (FASEB J) discloses "different copy numbers of an integrating TeP2 vector". Different copy numbers of the same gene can be considered a gene library. (see abstract of Griffith et al. (FASEB J.) , see page 47, col. 2 of Griffith et al. (FEBS Lett.)).

Applicant's arguments have been considered but have not been found convincing. Applicants have argued that the reference do not disclose at least one gene encoding an "unknown secreted protein". However, it is maintained that the term "unknown" is undefined and indefinite, and could be considered to encompass virtually any protein, since it appears to refer to the property of whether it is known to an observer. Therefore, the rejection is maintained.

Claims 23, 25, 26, 28, 39, 43 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al. (Embo J. 16, 6394-6406, 1997).

This rejection is maintained essentially for the reason made of record in the previous Office action.

Jones et al. discloses activation of a degP-lacZ reporter upon overproduction of either PapE or PapG. Page 6399 column 2 last paragraph, further states that "The presence of misfolded or partially denatured proteins in the periplasm is thought to be a signal that leads to activation of degP transcription". In fact degP is also known as htrA- , i.e. one of the genes, the promoter of which is proposed to be used for monitoring of secretion stress in the present application. In any case, the reference discloses

expression of several genes (I.e. a library) in a host where the activity of a promoter responsive to secretion stress can be monitored, and therefore, screened.

Applicant's arguments have been considered but have not been found convincing. Applicants have argued that the reference do not disclose at least one gene encoding an "unknown secreted protein". However, it is maintained that the term "unknown" is undefined and indefinite, and could be considered to encompass virtually any protein, since it appears to refer to the property of whether it is known to an observer. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30, 31, 33, 34, 36, 38, 41, 42, 45, 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lesley et al. (Protein Engineering Vol 15, No. 2, pp. 153-160, 2002) or Waldo (Curr Opin Chem Biol 2003, 7:33-38) in view of Noone et al. (J. Bacteriol. 183,b 2, 2001, 654-663) (all cited by applicants).

This rejection is maintained essentially for the reasons made of record in the previous Office action.

Lesley et al. or Waldo each teach the strategy of monitoring a host cell's response to protein overproduction by testing the activity of stress promoters linked to reporter genes. Many stress promoters (e.g. promoters of the heat shock response) respond to the presence of unfolded proteins in a cell, including unfolded proteins generated using overexpression strategies. In order to monitor such stress induced by unfolded proteins. a reporter gene is typically expressed under the control of e.g. a heat shock promoter. Clones (or growth conditions) that allow expression of a target protein without triggering the stress response can then be selected. Numerous genes are screened using the system (see page 156-158, Lesley et al.; see page 36 of Waldo). The instant application differs from Lesley et al. or Waldo in that secreted proteins are concerned. However Noone et al disclose the secretion stress promoter disclosed in the instant claims. It would have been obvious to one of ordinary skill in the art to have substituted the promoter disclosed by Noone et al. in the methods disclosed by Lesley et al. or Waldo, since all of the references disclose promoters operatively linked to reporter genes, that response to environmental conditions of stress induced by expression of particular types of proteins. One would have been motivated to do so by the desire to screen for secreted proteins, which is known to be useful for ease of production and purification of the protein produced. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Applicant's arguments filed 1/4/11 have been considered but have not been found convincing. Applicants have argued that the Examiner has failed to make a prima facie case of obviousness, since the examiner has not provided a reason of why the disclosures of the reference should be combined, and that the cited references are devoid of any suggestion to combine the teachings as advanced by the Examiner, except using the Applicant's disclosure by hindsight reasoning. However, it is maintained that one of ordinary skill in the art would recognize that any promoter which responds to the stress of producing a protein that is heterologous, and therefore is under some sort of unusual and non-natural conditions, would be useful for assaying for the presence of said protein, and that using a reporter gene under the control of said promoter, would allow one to assay for that production. Lesley et al. or Waldo et al. each disclose such an assay. Since Noone et al. disclose a promoter that responds to secretion stress, which is another type of 'stress" similar to the presence of the unfolded protein disclosed by Lesley et al or Waldo, one of ordinary skill in the art would have been motivated to use this promoter in a similar method. Therefore, it is maintained that there is adequate teaching when the references are considered in combination, for it to be obvious to one of ordinary skill in the art to modify the primary references by including the promoter of Noone et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama can be reached on (571) 272-2911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
3/13/11